REMARKS/ARGUMENTS

The Pending Claims

Claims 35, 39-42, 45-48, and 50-53 are pending and are directed to a method of changing the sensory perception of an animal.

The Amendments to the Claims

Claim 35 has been amended to clarify that the pharmaceutical composition comprises an adenoviral vector selected from the group consisting of adenoviral vector A, B, D, E, and F subgroups, to delete the term "specifically", and to correct matters of form. Claim 46 has been amended to comport with the language of claim 35. Accordingly, no new matter has been added by way of these amendments.

The Office Action

Claim 35 is objected to because of alleged informalities. Claims 35, 39-42, 45-48, and 50-53 remain rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Claims 35, 39-42, 45-48, and 50-53 remain rejected under 35 U.S.C. § 112, first paragraph, for allegedly introducing new matter into the disclosure of the present application. Claims 35, 39-42, 45-48, and 50-53 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Claims 35, 39, 40, 41, 42, 45-48, 50, 51, 52, and 53 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6,838,444 (Zoghbi et al. - "the Zoghbi patent") and U.S. Patent No. 5,837,511 (Falck-Pedersen et al. – "the Falck-Pedersen patent") alone, or in further view of U.S. Patent 6,821,775 (Kovesdi et al. - "the Kovesdi patent"), Staecker et al., *Otolaryngol. Head Neck Surg.*, *119*(1): 7-13 (1998) ("the Staecker reference"), U.S. Patent 6,455,314 (Wickham et al. - "the Wickham patent"), and/or Mizuguchi et al., *Gene Ther.*, *9*(12):769-776 (2002) ("the Mizuguchi reference"). Reconsideration of the objection and rejections is respectfully requested.

Examiner Interview

Applicants thank Examiner Shen for the courtesy extended to their representative, Melissa E. Kolom, during the telephonic interview held on December 8, 2008. The matters discussed during the interview are substantially as set forth herein.

Discussion of Claim Objection

Claim 35 is objected to because the term "Hath1" allegedly should not be italicized because it refers to a protein, rather than a gene. Claim 35 has been amended accordingly, thereby rendering this objection moot.

Discussion of Indefiniteness Rejection

The Office Action alleges that claims 35, 39-42, 45-48, and 50-53 are indefinite under Section 112, second paragraph, because the specification does not define the phrase "a promoter that specifically functions in supporting cells of the inner ear." As suggested by Examiner Shen during the aforementioned interview, the term "specifically" has been deleted from claim 35. As previously pointed out by Applicants, the specification defines tissue-specific promoters, including promoters that function in supporting cells of the inner ear (see specification at, e.g., paragraph 0055). Accordingly, the metes and bounds of claim 35, and claims depending therefrom, are clear. Therefore, Applicants request that the rejection under Section 112, second paragraph, be withdrawn.

Discussion of Rejections Under 35 U.S.C. 112, First Paragraph

Claims 35, 39-42, 45-48, and 50-53 are rejected under Section 112, first paragraph, as allegedly introducing new matter and lacking enablement. These rejections are traversed for the reasons set forth below.

A. New Matter

The Office Action alleges that the specification does not define the phrase "a promoter that specifically functions in the inner ear" and does not disclose any examples of such promoters. While the Office Action concedes that the application discloses that the hes-1 promoter functions in supporting cells, the Office Action alleges that the application does

not disclose that the activity of the hes-1 promoter is exclusive to supporting cells of the inner ear. While Applicants disagree with the Examiner's arguments, claim 35 has been amended to delete the term "specifically."

The specification defines a "tissue-specific" promoter as "a promoter that is preferentially activated in a given tissue and results in expression of a gene product in the tissue where activated" (see specification at, e.g., paragraph 0055). In addition, it was known in the art at the time the present application was filed that the *Hes1* gene is expressed in supporting cells of the inner ear and not in other cell types of the inner ear (see, e.g., Zheng et al., *Development*, *127*: 4551-4560 (2000)). Other genes that are expressed in supporting cells of the mammalian inner ear also were known in the art at the time the present application was filed (see Reply to Office Action dated July 24, 2008).

The Office Action also alleges that the specification does not disclose a subgroup A, B, D, E, or F adenoviral vector. In particular, the Office Action contends that the specification does not indicate that Applicants contemplated expression of a *Hath1* gene from an adenoviral vector of subgroup A, B, D, E, or F. Applicants respectfully disagree and note that the specification clearly discloses that the adenoviral vector can be of subgroup A, B, D, E, or F. In this regard, the specification states at paragraph 0024:

> an adenovirus can be of subgroup A (e.g., serotypes 12, 18, and 31), subgroup B (e.g., serotypes 3, 7, 11, 14, 16, 21, 34, 35, and 50), subgroup C (e.g., serotypes 1, 2, 5, and 6), subgroup D (e.g., serotypes 8, 9, 10, 13, 15, 17, 19, 20, 22-30, 32, 33, 36-39, and 42-48), subgroup E (e.g., serotype 4), subgroup F (e.g., serotypes 40 and 41), an unclassified serogroup (e.g., serotypes 49 and 51), or any other adenoviral serotype.

The specification further states at paragraph 0025:

> However, non-group C adenoviruses, and even non-human adenoviruses, can be used to prepare replication-deficient adenoviral gene transfer vectors for delivery of DNA to target cells in the inner ear. Preferred adenoviruses used in the construction of non-group C adenoviral gene transfer vectors include Ad12 (group A), Ad7 and Ad35 (group B), Ad30 and Ad36 (group D), Ad4 (group E), and Ad41 (group F).

For the foregoing reasons, the subject matter of the pending claims, as amended, is fully supported by the present application. Therefore, the subject matter of the pending claims does not introduce new matter into the present application, and the rejection under Section 112, first paragraph, should be withdrawn.

B. Enablement

The Office Action acknowledges that the specification enables a method of changing the sensory perception of an animal, which comprises administering to the inner ear a pharmaceutical composition comprising an adenoviral vector comprising a nucleic acid sequence encoding Hath1 operably linked to a promoter that drives gene expression in supporting cells of the inner ear. However, the Office Action alleges that the specification does not enable the method when the adenoviral vector comprises a nucleic acid sequence encoding Hath1 operably linked to a tissue specific promoter that drives expression *specifically* in the supporting cells of the inner ear.

While Applicants disagree with this rejection, claim 35 has been amended to delete the word "specifically" so as to generally comport the claim with what the Office Action concedes to be enabled by the specification. Thus, claim 35, as amended, recites a method of changing the sensory perception of an animal, wherein the method comprises administering to the inner ear a pharmaceutical composition comprising subgroup A, B, D, E, or F adenoviral vector, wherein the adenoviral vector comprises a nucleic acid sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the inner ear.

As discussed above, the specification defines a "tissue-specific" promoter as "a promoter that is preferentially activated in a given tissue and results in expression of a gene product in the tissue where activated" (see specification at, e.g., paragraph 0055). In addition, it was known in the art at the time the present application was filed that the *Hes1* gene is expressed in supporting cells of the inner ear and not in other cell types of the inner ear (see, e.g., Zheng et al., *Development*, *127*: 4551-4560 (2000)). Other genes that are expressed in supporting cells of the mammalian inner ear also were known in the art at the time the present application was filed (see "Reply to Office Action" dated July 24, 2008).

Accordingly, using the guidance provided by the specification in combination with the knowledge in the art at the time the present application was filed, one of ordinary skill in the art would be able to make and use the claimed invention without undue experimentation. Thus, Applicants request withdrawal of the enablement rejection under Section 112, first paragraph.

Discussion of Obviousness Rejection

Claims 35, 39, 40, 41, 42, 45-48, 50, 51, 52, and 53 are rejected under Section 103(a) as allegedly obvious over the Zoghbi patent and the Falck-Pedersen patent alone, or in further view of the Kovesdi patent, the Staecker reference, the Wickham patent, and/or the Mizuguchi reference. This rejection is traversed for the reasons set forth below.

For subject matter defined by a claim to be considered obvious, the Office must demonstrate that the differences between the claimed subject matter and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on certain factual inquiries including: (1) the scope and content of the prior art, (2) the level of ordinary skill in the prior art, (3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

Consideration of the aforementioned Graham factors here indicates that the present invention, as defined by the pending claims, is unobvious in view of the cited references.

Regarding the scope and content of the prior art, the Zoghbi patent discloses a method of generating hair cells in an animal (e.g., a human) comprising delivering to the inner ear of the animal a nucleic acid encoding an atonal-associated factor using, for example, an adenoviral vector. The Falck-Pedersen patent discloses methods for generating replication-deficient non-group C adenoviral vectors (i.e., subgroup A, B, D, E, and F).

The Kovesdi patent discloses an E1/E3/E4-deficient serotype 5 adenoviral vector encoding a pigment epithelium-derived factor (PEDF). The Staecker reference discloses a

method of transfecting auditory hair cells with an HSV vector encoding brain-derived neurotrophic factor. The Wickham patent discloses recombinant adenovirus fiber proteins that are modified to reduce affinity for the CAR cellular receptor. The Mizuguchi reference discloses adenoviral vectors that are ablated for binding to CAR and αv-integrin, as well as adenoviral vectors containing the RGD peptide inserted into the HI loop of the fiber knob.

For the sake of argument and for purposes of the present analysis, one of ordinary skill in the art can be assumed to be someone with an advanced degree and a few years of experience in the relevant art.

As acknowledged by the Office Action, the Zoghbi patent does not disclose the use of a non-group C adenoviral vector comprising a nucleic acid sequence encoding Hath1. Moreover, the Zoghbi reference does not disclose or suggest the use of an adenoviral vector which comprises a nucleic acid sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the inner ear. The Office Action argues that the Zoghbi patent suggests using a promoter that functions in supporting cells because the Zoghbi patent cites a publication (Zine et al.) which allegedly discloses that the *Hes1* gene is expressed in developing cochlea of inner ears. The Zine reference discloses that the Hes1 and Hes5 genes are expressed in the developing mouse cochleae, with the Hes5 gene expressed in supporting cells. Neither the Zine reference nor the Zoghbi patent, however, discloses or suggests employing promoters which function in supporting cells of the inner ear to control gene expression of the Hath1 gene in an adenoviral vector.

The Falck-Pedersen reference does not disclose or suggest the use of an adenoviral vector which comprises a nucleic acid sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the inner ear.

None of the secondary references cited by the Office Action discloses or suggests suggest an adenoviral vector which comprises a nucleic acid sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the inner ear, much less a method of using such an adenoviral vector to change the sensory perception of an animal. Therefore, the cited references, even in combination, do not disclose or suggest the subject matter defined by the pending claims.

Furthermore, the claimed invention involves surprising and unexpected results. In this regard, Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 of Douglas E. Brough, which discusses experimental results that demonstrate that a subgroup B adenoviral vector (i.e., Ad35) and a subgroup D adenoviral vector (i.e., Ad28) exhibit enhanced delivery to sensory cells of the inner ear as compared to a subgroup C adenoviral vector (i.e., Ad5).

Considering all of the Graham factors together, particularly the fact that the combination of the cited references do not disclose all of the elements of the pending claims, and that the claimed invention involves surprising and unexpected results, it is clear that the present invention would not have been obvious to one of ordinary skill in the art at the relevant time in view of the combination of cited references. Accordingly, the obviousness rejections under Section 103 should be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

Respectfully submitted,

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